

Fatal methadone toxicity: signs and circumstances, and the role of benzodiazepines

Abstract

Objective: To describe the signs and symptoms and circumstances of fatal methadone toxicity and investigate the role of benzodiazepines in these deaths.

Methods: Data were extracted from 1994 New South Wales (NSW) coronial files and cause of death established independently. Cases were grouped according to the likely source of methadone. Data describing the clinical history and circumstances of death were extracted from witnesses' and police statements.

Results: Methadone contributed to the deaths of 57 of the 87 adult coronial cases in which it was detected in NSW in 1994. The most commonly reported early signs of severe methadone toxicity were ataxia, slurred speech and evident euphoria. The late signs were unconsciousness, loud snoring and brown pulmonary oedema fluid coming from the mouth or nose. Death occurred an average 5.1 and 6.0 hours after oral ingestion and intravenous injection of methadone, respectively. Benzodiazepines were significantly more likely to have contributed to deaths from methadone toxicity among maintenance patients and people taking methadone tablets for pain relief than deaths involving diverted methadone syrup and deaths to which methadone did not contribute (OR 4.8, 95% CI 1.7 to 14.4).

Conclusions and implications: Benzodiazepines may contribute to deaths from methadone toxicity by increasing upper airways obstruction. Victims would have had a greater chance of survival if they had either been placed in the coma position or given mouth-to-mouth ventilation and an ambulance had been called. Benzodiazepines are more likely to contribute to fatal methadone toxicity in newly admitted maintenance patients and those taking methadone tablets for pain relief.

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A meta-analysis of five observational studies has found methadone maintenance reduces addicts' mortality by 75% by reducing the risk of fatal heroin toxicity.¹ However, maintenance programs are themselves a cause of fatal drug toxicity from prescribed doses of methadone and from diverted methadone syrup.²⁻⁴

In 1994, in New South Wales, a cluster of 10 deaths in the first two weeks of methadone maintenance caused addicts' risk of fatal drug toxicity to significantly increase after admission to treatment (RR first two weeks maintenance vs. 'on the streets' 6.7, 95% CI 3.3-13.9).^{2,3} However, as the weeks passed and patients developed a tolerance to the respiratory depressant effects of methadone, their risk of fatal drug toxicity fell dramatically (RR first two weeks vs. later maintenance 97.8, 95% CI 36.7-260.5).³

The first warnings^{5,6} and clinical reports^{7,8} of severe methadone toxicity soon followed the rapid expansion of New York City methadone maintenance programs in the early 1970s.⁹ Methadone toxicity was found to cause a profound hypoxia (lack of oxygen in the blood) and a severe pulmonary oedema.^{7,8,10,11} While the toxicity was generally reversed using an opioid antagonist, one group found that simply pumping air into their patients' lungs could save their lives.¹¹

As benzodiazepine abuse by methadone maintenance patients increased during the 1970s,^{12,13} benzodiazepines began to appear

in toxicology reports on both heroin- and methadone-related deaths. However, as benzodiazepines are relatively safe central nervous system depressants,^{14,15} their contribution to opioid-related deaths was initially not recognised. While it is now generally accepted that benzodiazepines can and frequently do contribute to fatal methadone toxicity,^{2,4,16,17} it is not clear how benzodiazepines interact with opioids/opiates to increase the risk of death.

To investigate this question and identify groups at particular risk, we undertook a detailed review of data collected from NSW coronial files on fatalities involving methadone. We also sought to describe the clinical course and circumstances of methadone toxicity.

Methods

Coronial cases in which methadone was detected in post-mortem specimens were identified from a database operated by the New South Wales (NSW) Attorney-General's Department. The search was limited to 1994 cases. The Coroner's files were examined by the principal author and summarised in a database. The Coroner's files contain the autopsy, toxicology and police reports and the statements of family and friends, treating doctors and other witnesses.

Cases were grouped according to the source of the methadone: methadone syrup given as maintenance treatment; methadone

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syrup diverted from maintenance programs; and methadone tablets prescribed for pain relief. Methadone maintenance patients were identified in a search of the database supervised by the NSW Health Department's Pharmaceutical Services Branch. The Drugs of Dependence Unit of the Queensland Health Department provided three methadone treatment histories. Where known illicit drug users died after taking methadone from an unknown source, this was assumed to be diverted methadone syrup.¹⁸

Subjects were classified as having taken methadone tablets when either a tablet bottle in their name was found, when the family indicated the deceased was taking methadone tablets or a pharmacist or doctor acknowledged the prescription. Two deaths, both suicides, were attributed to diverted methadone tablets because the deceased had professional access to methadone tablets but not syrup.

The likely causes of death were determined from the histories contained in the police and witnesses' statements and from the autopsy and toxicology reports (see Caplehorn and Drummer, 1999, for details). The authors initially established causes of death independently with OHD blind to the official determination. Causes of death were categorised as 'fatal drug toxicity – methadone contributed', 'fatal drug toxicity – methadone did not contribute' and 'other'. As there was very close agreement between the study and official causes of death,^{2,3} only results based on the study classification will be presented.

Attention was paid to factors known to be associated with situations physiologically similar to methadone toxicity, particularly sleep apnoea. Upper airways obstruction, as occurs in sleep apnoea, greatly increases the work of breathing as highly negative intrathoracic pressures are required to suck air past the obstruction.^{19,20} Research into sudden infant death syndrome suggests extreme negative pressures frequently cause petechiae on the surface of thoracic organs and subpleural intra-alveolar haemorrhages in the lungs.²¹ These features were sought in the autopsy reports.

The odds ratio was calculated exactly and its 95% confidence estimated using a mid-*p* correction (StatXact, 1991).²² The study was approved by the Western Sydney Area Health Service Human Research Ethics Committee and the NSW State Coroner.

Results

Methadone was detected in post-mortem material taken during coronial investigations into 89 deaths in NSW in 1994. The deaths of a neonate and an infant were excluded, leaving 87 adult cases. Of the 87, 41 were methadone maintenance patients, 28 most probably ingested methadone syrup diverted from methadone programs and 18 probably took methadone tablets (for details see Caplehorn and Drummer, 1999). Most were unemployed (49 of 87) males (66 of 87). Deaths involving methadone tablets were significantly more likely to have occurred in rural or regional NSW (7 of 18 vs. 9 of 69, $p=0.012$, chi-square) and to have involved older persons (mean age 43 years vs. 31 years, 95% CI difference in mean ages 6.5 to 19.7 years, *t*-test).

Methadone is thought to have contributed to 14 of the 41 deaths

among maintenance patients. Twelve of the 14 occurred during the first two weeks of maintenance treatment. Eight methadone patients died following trauma, five from natural causes and two were victims of homicide. Methadone did not contribute to six suicides and six cases of accidental drug toxicity among maintenance patients.

Methadone contributed to 26 of the 28 deaths involving diverted methadone syrup. The remaining two cases were a hanging and one of acute heroin toxicity.

Methadone contributed to 17 of the 18 cases involving methadone tablets. The remaining death was by hanging.

Overall, methadone is considered to have either caused or contributed to 57 deaths from accidental or deliberate drug toxicity; 'methadone deaths'. Methadone dose data of variable quality are available for 20 of the methadone deaths. The doses ranged from 10 mg to 200 mg, median 55 mg, mean 65.75 mg. Witness and police statements and autopsy reports suggest nearly all the maintenance- and tablet-related deaths involved oral ingestion of methadone (13 of 14 and 15 of 16 cases with data, respectively). Diverted methadone syrup was usually injected intravenously (16 of 24 cases with data).¹⁸

Almost all maintenance patients ingested the methadone at a dispensing facility (11 of 12 with data) while methadone tablets were generally taken when alone (15 of 15 with data). In more than half the cases involving diverted methadone syrup, it was ingested in the presence of friends (14 of 22 with data). In only one case was the body of a 'methadone death' found in a public place, 40 were found in their own or a friend's bed, and 14 elsewhere in their own or a friend's house. Most were found in the morning, between 0500 h and 1200 h (30 of 57).

In two cases death occurred more than a day after oral ingestion of methadone. When these two methadone deaths are excluded from calculations, the mean minimum time from oral ingestion to death was 5.1 hours (SD 3.8 hours, median 4.5 hours, $n=20$). The mean minimum time from intravenous injection of methadone to death was surprisingly similar, 6.0 hours (SD 4.4 hours, median 6 hours, $n=17$). However, four persons died within minutes of injecting methadone syrup intravenously.

Informative witness statements were available for 35 of the 57 methadone deaths. These statements were taken by police during unstructured interviews and contain witnesses' spontaneously reported observations. A majority of the witnesses were concerned about the deceased (21 of 35) and found they could not rouse them despite shaking, etc, (i.e. they were unconscious, 22 of 35). Witnesses commonly reported the deceased had been ataxic (13 of 35), had slurred speech (12 of 35), displayed evident euphoria (were 'really stoned', 23 of 35) or had been snoring loudly (20 of 35). Only a small minority (2 of 35) reported the deceased had vomited in the hours before they died.

Brown pulmonary oedema fluid was observed coming from the deceased's mouth or nose or was seen in the major airways at autopsy in 31 of the 57 methadone deaths. The autopsy revealed eight of the 57 methadone deaths had aspirated gastric contents and seven had intra-thoracic petechiae. Detailed autopsy reports

of the lungs were available in 52 of the 57 methadone deaths. These showed severe pulmonary oedema in 46 cases, eight of which also had areas of patchy broncho-pneumonia and 10 had intra-alveolar haemorrhages.

The post-mortem blood methadone concentrations for the methadone deaths ranged from zero to 5.5 mg/L, mean 0.53 mg/L (SD 0.74 mg/L, median 0.40 mg/L, $n=56$). (The zero post-mortem blood methadone concentration was caused by the deceased having survived for some days in a vegetative state in hospital. It was excluded from calculations.) Somewhat surprisingly, the mean blood methadone concentration in deaths not caused by drug toxicity (i.e. trauma, natural causes, etc) tended to be higher, mean 0.66 mg/L (SD 0.49 mg/L, median 0.59 mg/L, $n=22$).

Benzodiazepines contributed to 10 deaths among methadone patients. Eight of these occurred in the first two weeks of maintenance. Benzodiazepines were detected in post-mortem blood specimens in most of the methadone deaths involving either maintenance patients or methadone tablets (10 of 14 and 15 of 17, respectively). Benzodiazepines were detected in blood taken from slightly less than half the methadone deaths involving diverted methadone syrup and the 'non-methadone deaths' (12 of 26 and 14 of 30, respectively).

When the four groups were combined into two, the odds of benzodiazepines being detected in methadone deaths involving either maintenance patients or persons taking methadone tablets was 4.8 times the odds of their being detected in either methadone deaths involving diverted methadone syrup or non-methadone deaths (95% CI, OR 1.7-14.4, $p=0.003$). There was no apparent association between the detection of benzodiazepines and either reported snoring or pathological evidence of respiratory obstruction.

Five different benzodiazepines were detected in cases of fatal drug toxicity. The blood concentrations of these five drugs and the active metabolite nordiazepam were converted to a proportion of the concentration associated with serious toxicity in benzodiazepine-naïve adults: diazepam, 0.5 mg/L; temazepam, 0.6 mg/L; oxazepam, 0.3 mg/L; 7-aminoflunitrazepam, 0.04 mg/L; 7-aminoclonazepam, 0.05 mg/L; and, nordiazepam, 0.5 mg/L.²³⁻²⁵ The proportions of the toxic concentration for the five were added for each case to provide a summary statistic to express total proportion of toxic benzodiazepine concentration.

Considering only cases in which measurable concentrations of benzodiazepines were detected, there was no significant difference in the mean total proportion of toxic benzodiazepine concentration between methadone deaths involving either maintenance patients or persons taking methadone tablets, on the one hand, and either methadone deaths involving diverted methadone syrup or 'non-methadone' deaths, on the other (mean total proportion of potentially fatal concentrations 0.24 and 0.23, respectively).

Post-mortem blood benzodiazepine concentrations associated with fatal toxicity in benzodiazepine-naïve adults were found in five of the 57 methadone deaths: two methadone patients; two persons who took methadone tablets; and one who took diverted

syrup. Potentially fatal concentrations of benzodiazepines were also found in two deaths not due to drug toxicity.

Alcohol was detected in 12 of the 57 methadone deaths. In six cases the post-mortem blood alcohol concentration (BAC) was less than 0.10 gm/100 mL, between 0.15 and 0.20 gm/100 mL in three cases and more than 0.27 gm/100 mL in three cases. Alcohol is considered to have contributed to the six methadone deaths in which BAC was greater than 0.15 gm/100 mL. In three of these six cases the deceased injected diverted syrup, two took methadone tablets, and one was an established maintenance patient who died after injecting additional methadone (BAC=0.277 gm/100 mL).

Therapeutic and greater concentrations of benzodiazepines were detected in six methadone deaths involving alcohol, three with BAC less than 0.10 gm/100 mL and three with BAC greater than 0.15 gm/100 mL. Benzodiazepines probably contributed to two of the former and three of the latter deaths.

Discussion

Methadone was detected during coronial investigation of the deaths of 87 adults in New South Wales in 1994. Methadone most probably contributed to 57 deaths from drug toxicity: 14 maintenance patients; 17 persons who took methadone tablets; and 26 illicit drug users who ingested methadone syrup diverted from maintenance programs.

Generally, adults who died of methadone toxicity were known to be very intoxicated before going to bed. The signs most commonly reported by family and friends were a staggering walk, slurred speech and evident euphoria. Once in bed, the deceased typically snored loudly, were unconscious for hours and often had brown, frothy oedema fluid coming from their mouth or nose.^{2,3,16,17} While persons in this condition are critically ill, one young man spontaneously and fully recovered. (He unfortunately tried to repeat the experience three days later and died.)

As fatal toxicity generally took several hours to develop after both oral ingestion and intravenous injection of methadone, friends or family members had time to become concerned about the deceased and attempt to care for them.^{3,17} Unfortunately, these attempts failed as the helpers did not realise the seriousness of the situation and did not call an ambulance or attempt mouth-to-mouth ventilation.

To reduce the number of deaths, methadone program staff, patients and their families need to be better informed about the signs of methadone toxicity and the appropriate responses.² Currently, it seems not only the public but also methadone program staff are ill-informed. A recent survey of 149 US maintenance program staff showed most had difficulty answering six basic questions on methadone toxicity.²⁶

While the estimates of deaths associated with methadone maintenance are believed to be relatively accurate, the number of deaths associated with methadone tablets must have been severely under-estimated. This is because every case the local doctor thought might be an unnatural death (i.e. a coroner's case) was a case of fatal methadone toxicity. As none of the deaths involving

methadone tablets were due to natural causes, the local doctors' classification had a specificity of 100%. This is only possible if most cases of unnatural, methadone-related death were missed, i.e. the sensitivity of the doctors' classification was low. It is likely many local doctors assumed their patients died from the cause of the chronic pain (i.e. natural causes) rather than from the adverse effects of treatment (i.e. an unnatural, fatal drug toxicity).

As a crude clinical classification with 100% specificity is likely to have a sensitivity of at best 33%, it is likely that over 50 chronic pain patients died from the toxic effects of methadone tablets in NSW in 1994. In terms of the number of persons who died, benzodiazepines were most dangerous to chronic pain patients. Based on the estimate of more than 50 deaths and assuming that benzodiazepines contributed to the same proportion of deaths, we estimate that approximately 40 chronic pain patients died from the combined effects of benzodiazepines and methadone tablets in NSW in 1994.

Benzodiazepines were significantly more likely to be detected in methadone deaths involving either maintenance patients or chronic pain patients taking methadone tablets than in deaths caused by either diverted methadone syrup or deaths to which methadone did not contribute (OR 4.8, 95% CI 1.7-14.4). As the overwhelming majority of the maintenance patients were in the first two weeks of maintenance treatment (12 of 14), benzodiazepines are most dangerous early in maintenance.

The increased likelihood of benzodiazepines being detected in those dying from methadone toxicity early in maintenance and in chronic pain patients suggests benzodiazepines are most dangerous in persons without a tolerance to opioids who take repeated doses of methadone, i.e. benzodiazepines are more likely to contribute to cases of cumulative methadone toxicity in non-tolerant individuals. However, the demonstration of a statistical association does not establish a causal relationship. Moreover, the association was tested *post hoc* and should be tested as an *a priori* hypothesis in another study of a group of methadone-related deaths.

Surprisingly, the effect of benzodiazepines did not seem to be related to the post-mortem blood concentration. Indeed, relatively low concentrations of benzodiazepines seemed to contribute to methadone toxicity. As only therapeutic concentrations of benzodiazepines are needed to relax muscle whereas high concentrations are required to produce significant respiratory depression, this suggests benzodiazepines act primarily by relaxing the muscles controlling the upper airway, causing respiratory obstruction.

This suggestion is biologically plausible. Occlusion of the upper airway is more likely to be important in a person suffering a slowly developing, cumulative toxicity, rather than an acute, overwhelming opioid overdose. Other authors have similarly suggested benzodiazepines increase the risk of sudden death in sleep apnoea by increasing upper airways obstruction.^{27,28} Methadone toxicity, like sleep apnoea, causes severe hypoventilation. Even stable doses of methadone can cause daytime hypoventilation and hypercapnia^{29,30} and cause sleep-disordered breathing and even sleep apnoea in established maintenance patients.³¹ However, our

conclusion regarding respiratory obstruction is essentially speculative and requires further investigation.

While more work is needed to clarify the issues, our suggestions have several important, practical implications. Persons caring for a victim of slowly developing methadone toxicity would greatly improve the situation by placing them in the coma position and tilting their head back. In more serious situations, where the victim is still not breathing adequately, mouth-to-mouth ventilation will be required until the arrival of an ambulance.

Research is urgently needed into the relative safety of methadone and other orally effective opioid analgesics, e.g. oxycodone. Methadone is unusual in that its respiratory depressant effects last much longer than its analgesic effects. One double-blind trial of intravenous morphine and methadone in cancer patients found there was no difference in the duration of analgesia, mean four hours.³² Daily doses of methadone depress respiration for the 24 hours between doses and the effects are cumulative.²⁹⁻³¹ If patients experiencing pain took methadone tablets every six hours, their respiration would be progressively depressed over the first days and even weeks of treatment.²⁹⁻³¹ If they had pre-existing sleep disordered breathing or lung disease they would be at particular risk of fatal methadone toxicity. Consequently, it is likely that opioids with approximately equal durations of respiratory depression and analgesia, e.g. oxycodone, are safer than methadone.

Doctors and patients should be warned that even therapeutic doses of benzodiazepines may increase the risk of fatal drug toxicity in new admissions to methadone maintenance and in patients taking methadone tablets intermittently for pain relief. Heroin addicts who abuse benzodiazepines should be given low starting doses of methadone and very gradual dose increases. Where this may cause unacceptable discomfort from opioid withdrawal, they should be offered in-patient induction of maintenance treatment.

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Commentary

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As in their previous reports, these authors meticulously document mortality findings related to the world's most popular heroin addiction treatment. Corroborating the findings of others, these include:

- a low overall mortality in methadone maintenance patients of around 0.6% per year;
- extreme rarity of prescribed methadone contributing to death after the first two weeks of treatment (approx. 0.03% per year);
- excess mortality in the first two weeks of treatment;
- very high rates of alcohol and sedative use in opioid overdoses; and
- disproportionately high mortality from methadone tablets prescribed unsupervised for chronic pain treatment.

These authors have repeated serious criticism of some clinical practices.^{1,2} Four years should have been ample time to collaborate with practising clinicians but this seems not to have occurred.³ Nor have the authors adequately addressed questions raised about the definition of 'iatrogenic methadone toxicity' and why their findings were often discrepant from official Coroner's reports.⁴

Assessments and dose inductions are crucial due to two competing factors, toxicity and drop-outs. When following clinical guidelines toxicity is rare, although drop-outs occur commonly. Some of these are due to inadequate dosing, especially in the first two weeks. In their discussion, these authors do not address treatment drop-outs and their known excessive mortality.⁵

It is also unfortunate that with their speculation on sleep disorders that they have not collaborated with experts in this complex field. Their evidence for a sleep-apnoea like syndrome is tantalising if not very substantial.

Two findings that the authors found 'surprising' were that blood levels of neither methadone nor benzodiazepines corresponded with clinical toxicity. Indeed, those who were found to have died from methadone toxicity had substantially lower blood levels than methadone patients who died from causes other than poisoning (0.53mg/L vs. 0.66mg/L). Also, while five of 57 'methadone deaths' also had potentially fatal benzodiazepine levels, so too did two of 30 who died from non-poisoning causes. Thus many patients may tolerate very high drug levels without apparent clinical toxicity. It was Capplehorn's own work which demonstrated a protective effect from methadone treatment.⁶

There can be little doubt that the use of benzodiazepines and alcohol can increase opioid overdose mortality. The influence of such depressants in these deaths is probably largely due to a combination of their effects on mood, behaviour, memory, judgement and coordination. There may also be direct effects on the airway and respiratory muscles, especially at high blood levels. But even relatively low levels seem to increase the risk in those injecting heroin. Injecting requires both judgement and good locomotor skills. Capplehorn and Drummer concentrate on a theoretical